

vol. 93, p. 12969-73), and further in view of U.S. Patent No. 5,607,967 to Friedman et al. and Gurtu et al. (Biochem Biophys Res Commun, vol. 229, p. 295-8).

The foregoing constitutes the entirety of the rejections raised in the September 25, 2002 Official Action. In light of the present amendments and the following remarks, each of the above-mentioned rejections under 35 U.S.C. §112, second paragraph and 35 U.S.C. §103(a) is respectfully traversed.

CLAIMS 1-3 FULLY COMPLY WITH THE REQUIREMENTS OF 35 U.S.C.

§112, SECOND PARAGRAPH

The relevant inquiry in determining whether a given claim satisfies the requirements of 35 U.S.C. §112, second paragraph, is whether the claim sets out and circumscribes a particular area with a reasonable degree of precision and particularity such that the metes and bounds of the claimed invention are reasonably clear. In re Moore, 169 U.S.P.Q. 236 (CCPA 1971). Applicants respectfully submit that with respect to claims 1-3 this inquiry must be answered in the affirmative.

With regard to the term "recombinant cell(s)" which is recited in claims 1 and 3, Applicants submit that a skilled artisan would readily appreciate the metes and bounds of this phrase. Indeed, Merriam-Webster's Collegiate® Dictionary defines a recombinant cell as a cell "containing recombinant DNA," and the latter expression is defined as "genetically engineered DNA prepared in vitro by cutting up DNA molecules and splicing together specific DNA fragments." Therefore, the expression "recombinant cell line" (which is the terminology of the claim in question) can refer to a stably transfected cell line. Moreover, a search of www.yahoo.com for the phrase "recombinant cell" produced over 1,100 matches. The Genetics 2 PowerPoint® presentation from Western Connecticut State University (match #19 from the www.yahoo.com search) has been provided to further clarify the term "recombinant cell" (see

page 14). Accordingly, Applicants submit that the metes and bounds of claims 1 and 3 with regards to the terms "recombinant cell line" and "recombinant cells" are clear and request that rejection of these claims under 35 U.S.C. §112, second paragraph be withdrawn.

The Examiner also asserts that the phrase "p300" in claims 1-3 is unclear as to whether "p300" refers to a specific protein or to a family of transcriptional coactivators referred to in the art as CBP/p300 or p300/CBP. The Examiner has assumed that the latter is intended. In keeping with the Examiner's assumption, applicants have amended claims 1-3 to contain the phrase "p300/CBP" in place of "p300" for referencing this particular family of transcriptional coactivators in order to eliminate the ambiguity perceived by the Examiner. Support for the amendments can be found, as noted by the Examiner, at page 15, line 27 to page 16, line 20 of the instant application.

The Examiner also asserts that the expressions "a p300 responsive promoter" and "a non p300 responsive promoter" which are recited in claims 1-3 are unclear in terms of their metes and bounds. The Examiner also questions whether the mdm2 promoter of Gu et al. is within the metes and bounds of "a p300 responsive promoter." Applicants disagree with the Examiner's position with regard to the clarity of the expression "a p300 responsive promoter." Applicants respectfully direct the Examiner's attention to page 22, lines 25-26 of the present specification which discloses the following: "a plasmid containing a p300 regulated promoter, such as the mdm2 promoter." This indicates quite clearly that the mdm2 promoter of Gu et al. is indeed "a p300 responsive promoter." At page 23, lines 15-21, the present specification also discloses that the cells to be used to characterize the panel of compounds are "transfected with a plasmid containing a reporter gene operably linked to a promoter which is transactivated by p300. An exemplary promoter is the mdm2

promoter." In light of the foregoing, Applicants submit that the metes and bounds of "a p300 responsive promoter" are clearly disclosed as a promoter that is transactivated by p300 or, as acknowledged by the Examiner, a promoter whose activity is increased in the presence of p300.

Applicants also take exception to the Examiner's position with regard to the alleged lack of clarity of the expression "a non p300 responsive promoter." Specifically, Applicants note that the specification discloses that the cells used to characterize the panel of compounds are "co-transfected with a control plasmid containing a second reporter operably linked to a non p300 responsive promoter" (page 23, lines 15-21). Based on its use as a control for a promoter that is transactivated by p300, a skilled artisan would clearly appreciate that the non p300 responsive promoter is one that is not transactivated by p300 or, as acknowledged by the Examiner, one whose activity is not increased in the presence of p300.

The Examiner also questions whether the promoter, MG₁₅-CAT of Lill et al. is within the metes and bounds of "a non p300 responsive promoter." Applicants contend that the description within Lill et al. of the promoter is insufficient to determine whether the promoter is, indeed, a "non p300 responsive promoter" because the relative activity of the promoter was not assessed in the presence of increased p300 protein levels. Applicants believe, however, that the promoter MG₁₅-CAT would likely qualify as "a non p300 responsive promoter" because the DNA binding protein p53 which tethers p300 to the wild-type PG₁₃-CAT promoter is no longer capable of effectively binding the MG₁₅-CAT promoter. Therefore p300 protein levels likely have no effect on the activity of the MG₁₅-CAT promoter.

The Examiner also contends that it is "not trivial to tell which promoter is more active in the presence of p300 and which promoter is not responsive to p300." Applicants

strenuously disagree with the Examiner in this regard. Indeed, Gu et al. teaches transfecting cells with a plasmid containing a promoter operably linked to reporter gene (mdm2-luc) with or without a plasmid expressing CBP (page 820, column 1 and Figure 3). Comparison of the amounts of reporter protein 30 hours later revealed that the activity of the promoter was greater in the presence of CBP than in the absence of CBP indicating the promoter was "a p300 responsive promoter." It would be immediately apparent to a skilled artisan that if the expression of the reporter gene had not increased, then the promoter would be "a non p300 responsive promoter."

In light of the foregoing, Applicants respectfully request the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

CLAIMS 1-3 ARE NOT RENDERED OBVIOUS BY THE COMBINATION OF LILL ET AL., GU ET AL., OR ARANY ET AL. AND U.S. PATENT 5,607,967 AND GURTU ET AL.

The Examiner has rejected claims 1-3 under 35 U.S.C. §103(a) as allegedly being unpatentable over Lill et al., Gu et al., or Arany et al., and further in view of U.S. Patent No. 5,607,967 and Gurtu et al. Specifically, the Examiner contends that Gu et al., Lill et al., and Arany et al. disclose recombinant cells comprising a plasmid that contains either i) a DNA enhancer/promoter linked to a reporter gene whose activity is increased in the presence of p300 or ii) a plasmid that contains a DNA enhancer/promoter linked to a reporter gene whose activity is not increased in the presence of p300. The Examiner concedes that none of the above three references discloses a screening method for compounds of interest, but asserts that U.S. Patent No. 5,607,967 does teach a screening method using a recombinant cell comprising a promoter linked to a reporter gene. The Examiner also concedes that none of the above four references teaches stably transfected cells expressing two reporter genes and a

selectable marker gene, but claims Gurtu et al. teaches that the stable transfection of mammalian cells is a widely established technique. The Examiner then concludes from the disclosures of the above five references that it would have been obvious to one of ordinary skill in the art, at the time the claimed invention was made, to combine the teachings of these references to arrive at the instant invention. Applicants strenuously disagree with the Examiner's assessment of the prior art, as the cited references clearly fail to teach or suggest all of the instant claim recitations and fails to provide the necessary suggestion or motivation to produce the invention claimed in the instant application.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claimed limitations (MPEP §2143).

At the outset, Applicants submit that the Examiner's interpretation of Lill et al. in the September 25, 2002 Official Action is plainly in error. Specifically, the Examiner asserts that Lill et al. teaches at page 823, right column of a "recombinant cell comprising ... a plasmid expressing a mutated promoter operatively linked to a reporter gene, CAT reporter gene, i.e. MG₁₅-CAT, and a second plasmid expressing wild-type p300/CBP promoter." Applicants disagree with this assertion and note that the cells referred to by the Examiner are transiently transfected with a plasmid comprising a mutated promoter operably linked to a reporter gene and a plasmid expressing p300 **protein**.

A relevant inquiry in determining obviousness under 35 U.S.C. §103 based on the combined disclosure of references, is

whether the references supply some teaching or suggestion to one of ordinary skill in the art to arrive at the invention as claimed. In re Dow Chemical Company, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the teaching or suggestion supporting the desirability or the combination must be found in the prior art, not in the applicant's disclosure. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Under these standards, none of the cited references, considered singly or in combination, renders obvious the invention as claimed in claims 1-3.

Gu et al. disclose cells transiently transfected with i) a plasmid expressing CBP and ii) a plasmid containing a DNA enhancer/promoter element, linked to a reporter gene, whose activity is increased in the presence of CBP and thus this reference like the others relied on by the Examiner fails to provide an important negative control for the instantly claimed screening methods. Importantly, Gu et al. fails to teach or suggest of a plasmid containing a DNA enhancer/promoter element, linked to a second reporter gene, whose activity is not increased in the presence of CBP. Applicants also submit that Gu et al. does not provide motivation to screen compounds to test for their ability to inhibit p300 transactivation and thereby induce apoptotic cell death.

Lill et al. disclose cells transiently transfected with i) a plasmid expressing p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to a reporter gene, whose activity is increased in the presence of p300. Lill et al. also disclose cells transiently transfected with i) a plasmid expressing p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to the same reporter gene, whose activity is not increased in the presence of p300.

Applicants note, however, that nowhere does Lill et al. teach or suggest of a recombinant cell comprising of both i) a plasmid containing a DNA enhancer/promoter element, linked to a reporter gene, whose activity is increased in the presence of p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to a second reporter gene, whose activity is not increased in the presence of p300. Applicants also submit that nowhere in the disclosure by Lill et al. is there a suggestion that p300 transactivation could be used as a target for screening compounds for the induction of apoptosis.

Arany et al. also disclose cells transiently transfected with i) a plasmid expressing p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to a reporter gene, whose activity is either increased in the presence of p300 or not affected by the presence of p300. Applicants respectfully submit, however, that at no point does Arany et al. teach or suggest of a recombinant cell comprising i) a plasmid containing a DNA enhancer/promoter element, linked to a reporter gene, whose activity is increased in the presence of p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to a second reporter gene, whose activity is not increased in the presence of p300. The Examiner asserts that Arany et al. also teaches that a "p300 protein complex that activates transcription could be a therapeutic target for the treatment of cancer." Closer inspection of the reference, however, shows that Arany et al. specifically refers to a "p300/CBP-HIF complex" as a possible target for "disorders characterized by aberrant hypoxia-induced neovascularization." Applicants submit that at no point does Arany et al. suggest p300 is a possible target for the regulation of apoptosis or suggest that p300 could be a possible target in the absence of HIF.

In summary, Applicants submit that the above three references fail to describe or suggest a recombinant cell comprising i) a plasmid containing a DNA enhancer/promoter

element, linked to a reporter gene, whose activity is increased in the presence of p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to a second reporter gene, whose activity is not increased in the presence of p300. Thus these references, when considered singly or in combination, fail to provide sufficient motivation to develop recombinant cells lines suitable for screening a panel of compounds to identify agents which inhibit p300 transactivation and thereby induce apoptotic cell death.

The Examiner's reliance on U.S. Patent 5,607,967 to Friedman et al. is clearly misplaced. Friedman et al. discloses a recombinant cell expressing a chimeric protein consisting of a human steroid hormone receptor and a DNA binding domain from a "known ligand-responsive receptor protein." These recombinant cells are transfected with a plasmid containing a promoter region, linked to reporter gene, which contains a specific binding site for the DNA binding domain of the chimeric protein. Friedman et al. also discloses a method for challenging these cells with a panel of compounds and monitoring the reporter gene to assess activation of the steroid hormone receptor domain of the chimeric protein. It is clear, however, that Friedman, et al. fails to describe or suggest transfecting cells with another plasmid containing another promoter element, linked to a second reporter gene, which is not responsive to the chimeric protein. Applicants also note that Friedman et al. teaches a method for screening compounds for the modulation of transcriptional activators which directly bind DNA. p300 is a transactivator that modulates transcription by being tethered to DNA by DNA binding proteins or other means. Friedman et al. provides no motivation or suggestion for extrapolating the disclosed method directed to DNA binding proteins to such transactivators.

Gurtu et al. disclose a method to generate a stable cell line by transfecting cells with a plasmid encoding a gene of

interest followed by an internal ribosome entry site linked to an antibiotic resistance marker. The Examiner contends that "this teaching suggests that if two different reporter genes are used, then it is less time consuming and more straight forward to select clones that are transfected with multiple plasmids." Applicants respectfully take exception to the Examiner's interpretation of Gurtu et al. There is nothing in Gurtu et al. to suggest creating a stable cell line by transfecting two plasmids containing two unique antibiotic resistance genes and selecting for recombinant cells expressing both plasmids by maintaining the cells in the appropriate antibiotics. Indeed, Gurtu et al. teaches only the transfection of a single plasmid containing the gene of interest operably linked to a selection gene by an internal ribosome entry site.

Considering the fundamental differences between the claimed invention and the various references alleged to provide evidence of unpatentability in this case, the conclusion is inescapable that the Examiner has impermissibly engaged in hindsight reconstruction of the claimed invention. It is quite apparent that the Examiner has used the Applicant's disclosure as a guide for combining unrelated prior art disclosures in an effort to establish a case of obviousness. None of the cited prior art references provide the necessary motivation to combine the teachings of these disclosures to arrive at the invention as claimed in claims 1-3. Since none of these references provide specific motivation for combining their teachings to arrive at the claimed invention, Applicants are unaware of any other way the Examiner could possibly have combined these references to arrive at the claimed invention without using the Applicants' disclosure as a template.

Additionally, even if the disparate teachings of the various references were properly combinable in the manner proposed by the Examiner (which Applicants vigorously dispute)

the resultant combination of references still fails to teach or suggest all of the claim limitations of the instant application. Specifically, the cited references fail to teach or suggest a recombinant cell comprising i) a plasmid containing a DNA enhancer/promoter element, linked to a reporter gene, whose activity is increased in the presence of p300 and ii) a plasmid containing a DNA enhancer/promoter element, linked to a second reporter gene, whose activity is not increased in the presence of p300.

Moreover, the requirement for a reasonable expectation of success to establish a *prima facie* case of obviousness is not met because the cited references, alone or in combination, fail to teach or suggest all of the claim limitations of the instant application.

In summary, Applicants respectfully submit that the rejection of claims 1-3 under 35 U.S.C. §103(a) is untenable and must be withdrawn.

CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the September 25, 2002 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation
By Kathleen D. Rigant
Kathleen D. Rigant, Ph.D., J.D.

PTO Registration No. 43,047

Telephone: (215) 563-4100

Facsimile: (215) 563-4044

Enclosure: -Marked up draft of amended claims and web pages

Marked up draft of amended claims

1. A recombinant cell line for assessing therapeutic agents that regulate apoptosis, comprising:

- a) a first plasmid expressing a p300/CBP responsive promoter operably linked to a first reporter gene;
- b) a second plasmid expressing a non p300/CBP responsive promoter operably linked to a second reporter gene; and
- c) a third plasmid expressing a selectable marker gene.

2. The cell line of claim 1, said cell line being stably transfected with an additional plasmid encoding wild-type p300/CBP to augment endogenously expressed p300/CBP protein levels.

3. A screening method for determining if a therapeutic reagent inhibits p300/CBP activity thereby inducing apoptosis, comprising:

- a) contacting recombinant cells with said therapeutic agent, said cells containing
 - i) a first plasmid expressing a p300/CBP responsive promoter operably linked to a first reporter gene;
 - ii) a second plasmid expressing a non p300/CBP responsive promoter operably linked to a second reporter gene; and
 - iii) a third plasmid expressing a selectable marker gene;
- b) assessing cells for repression of the p300/CBP responsive reporter gene by said therapeutic reagent; and
- c) assessing cells for repression of the non-p300/CBP responsive reporter gene by said therapeutic reagent, repression in step b) and not step c) indicating that the compound inhibits p300/CBP transactivation and thereby induces apoptosis.